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<p>(21) International Application Number: PCT/EP97/07035</p> <p>(22) International Filing Date: 15 December 1997 (15.12.97)</p> <p>(30) Priority Data: 9627005.3 27 December 1996 (27.12.96) GB</p> <p>(71) Applicant (for all designated States except US): KNOLL AK- TIENGESSELLSCHAFT [DE/DE]; Knollstrasse, D-67061 Ludwigshafen (DE).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): BIRCH, Alan, Martin [GB/GB]; R5 Pennyfoot Street, Nottingham, Notting- hamshire NG1 1GF (GB). BRADLEY, Paul, Anthony [GB/GB]; R5 Pennyfoot Street, Nottingham, Notting- hamshire NG1 1GF (GB).</p> <p>(74) Agent: MILLER, Thomas, Kerr; BASF Aktiengesellschaft, D-67056 Ludwigshafen (DE).</p>		<p>(81) Designated States: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HU, ID, IL, JP, KR, KZ, LT, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: HETEROARYLSULFONAMIDE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM</p> <div data-bbox="597 1129 1055 1291" data-label="Chemical-Block"> <p style="text-align: center;">(I)</p> </div> <p>(57) Abstract</p> <p>Compounds of formula (I) and pharmaceutically acceptable salts thereof in which A is methylene or -O-; B is methylene or -O-; G₁-G₂-G₃ form a heteroaromatic or heteroaliphatic chain; g is 0, 1 or 2; U is an alkylene chain optionally substituted by one or more alkyl; Q represents a divalent group containing nitrogen atoms; and T is an optionally substituted aryl or heteroaryl group, have utility in the treatment of central nervous system disorders, for example depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders and anorexia, cardiovascular and cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, and spasticity.</p>		

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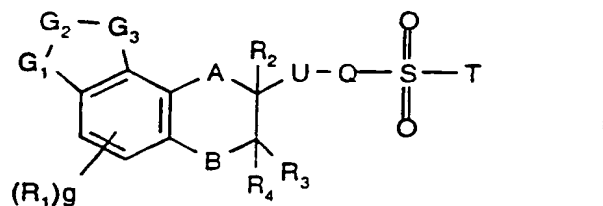
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HETEROARYLSULFONAMIDE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention relates to novel heteroarylsulphonamide compounds which have affinity for 5-HT_{1A} and/or D₂-like (D₂, D₃ and D₄ sub-types) receptors, to processes for their preparation, to pharmaceutical compositions containing them and to their use in the treatment of central nervous system disorders, for example depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders and anorexia, cardiovascular and cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, and spasticity.

The present invention provides compounds of formula I



including enantiomers and pharmaceutically acceptable salts thereof in which

A is methylene or -O-;

B is methylene or -O-;

G₁-G₂-G₃ represent -N(R')-C(R'')=N-, -N=C(R'')-N(R')-, -N(R')-C(R'')=C(R''')-,
-C(R''')=C(R'')-N(R')-, -N(R')-N=C(R'')-, -C(R'')=N-N(R')-, -N(R')-N=N-, -N=N-N(R')-,
-N=C(R'')-O-, -N=C(R'')-S-, -O-C(R'')=N-, -S-C(R'')=N-, -O-N=C(R'')-, -S-N=C(R'')-,
-C(R'')=N-O-, -C(R'')=N-S-, -S-C(R'')=C(R''')-, -C(R'')=C(R''')-S-, -O-C(R'')=C(R''')-,
-C(R'')=C(R''')-O- or -O-C(R')(R')-O-;

R' is H or an alkyl group containing 1 to 3 carbon atoms;

- R'' and R''', which are the same or different, are H; halo; an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo; carboxy; an alkanoyl group containing 1 to 6 carbon atoms; an alkoxycarbonyl group in which the alkoxy group contains 1 to 3 carbon atoms; formyl; cyano; or a carbamoyl group or carbamoylmethyl group each optionally *N*-substituted by one or two alkyl groups, which may be the same or different, each containing 1 to 3 carbon atoms;

g is 0, 1 or 2;

- 10 R₁ represents an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo; an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo; halo; or an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo; the substituents represented by R₁ being the same or different when g is 2;

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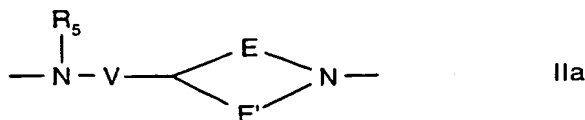
R₂ is H or an alkyl group containing 1 to 3 carbon atoms;

R₃ and R₄, which are the same or different, are H, or an alkyl group containing 1 to 3 carbon atoms;

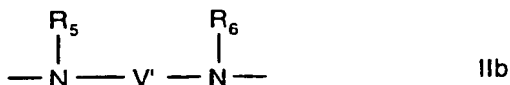
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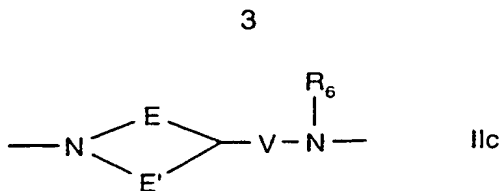
U is an alkylene chain containing 1 to 3 carbon atoms, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

Q represents a divalent group of formula IIa, IIb or IIc



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in which V is (CH₂)_n, wherein n is 0, 1, 2 or 3, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

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V' is an alkylene chain containing 2 to 6 carbon atoms, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

E is an alkylene chain containing 0 to 2 carbon atoms and E' is an alkylene chain containing 1 to 4 carbon atoms provided that the total number of carbon atoms in E and E' amounts to 3 or 4;

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R₅ and R₆, which may be the same or different, are H or an alkyl group containing 1 to 4 carbon atoms; and

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T represents phenyl, 1- or 2-naphthyl, 1-naphth[2,1-d][1,2,3]oxadiazolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-thienyl, 2- or 3-furyl, 2-, 3- or 7-benzo[b]furanyl, 2,3-dihydro-7-benzo[b]furanyl, 2-, 3- or 7-benzo[b]thiophenyl, 3-, 4- or 5-pyrazolyl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-2-yl, 5-tetrazolyl, 2-, 3- or 4-quinolinyl, 2- or 4-quinazolinyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isothiazolyl or 2-, 4- or 5-thiazolyl each of which may be optionally substituted by one or more substituents selected from a) halo, b) an alkyl group containing 1 to 4 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g) hydroxymethyl, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alkoxy carbonyl group containing 2 to 6 carbon atoms, k) a carbamoyl group or carbamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphonamoyl or sulphonamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, m) an amino group optionally substituted by one or two

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alkyl groups each containing 1 to 5 carbon atoms, n) 1-pyrrolidinyl or 1-piperidinyl, o) nitro or p) acetamido.

In preferred compounds of formula I, A is -O-.

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In preferred compounds of formula I, B is -O-.

In more preferred compounds of formula I, both A and B are -O-.

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In preferred compounds of formula I, g is 0 or 1. When g is 1, R₁ is preferably halo or an alkyl group containing 1 to 3 carbon atoms. In more preferred compounds of formula I, g is 0.

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In preferred compounds of formula I, G₁-G₂-G₃ are -NH-CH=CH-; -O-CH=CH-; or -S-C(R'')=C(R''')-. Preferably, R'' is H and R''' is H or halo (more preferably chloro). More preferably G₁-G₂-G₃ are -NH-CH=CH-; or -S-C(R'')=C(R''')-.

In preferred compounds of formula I, R₂ is H.

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In preferred compounds of formula I, R₃ and R₄, are both H.

In preferred compounds of formula I, U is methylene.

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In preferred compounds of formula I, Q is a group of formula IIc in which V is methylene, E and E' are both ethylene and R₆ is H.

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In preferred compounds of formula I, T is phenyl or 2-, 3- or 4-pyridyl each of which may be optionally substituted by one or more substituents selected from methoxy, nitro, halo or acetamido. In more preferred compounds of formula I, T is 2-pyridyl or 4-acetamidophenyl.

In one group of preferred compounds of formula I, both A and B are -O-; g is 1, R₁ is halo or an alkyl group containing 1 to 3 carbon atoms; G₁-G₂-G₃ are -NH-CH=CH-;

-O-CH=CH- or -S-C(R'')=C(R''')-; R'' is H and R''' is H or halo; R₂ is H; R₃ and R₄, are both H; U is methylene; Q is a group of formula IIc in which V is methylene, E and E' are both ethylene and R₆ is H; and T is phenyl or 2-, 3- or 4 pyridyl each of which may be optionally substituted by one or more substituents selected from methoxy, nitro, halo or acetamido.

In second group of preferred compounds of formula I, both A and B are -O-; g is 1, R₁ is halo or an alkyl group containing 1 to 3 carbon atoms; G₁-G₂-G₃ are -NH-CH=CH-; or -S-C(R'')=C(R''')-; R'' is H and R''' is H or halo; R₂ is H; R₃ and R₄, are both H; U is methylene; Q is a group of formula IIc in which V is methylene, E and E' are both ethylene and R₆ is H; and T is phenyl or 2-, 3- or 4 pyridyl each of which may be optionally substituted by one or more substituents selected from methoxy, nitro, halo or acetamido.

Compounds of formula I may exist as salts with pharmaceutically acceptable acids. Examples of such salts include hydrochlorides, hydrobromides, sulphates, methanesulphonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid. Compounds of formula I and their salts may exist in the form of solvates (for example hydrates).

It will be understood that any group mentioned herein which contains a chain of three or more atoms signifies a group in which the chain may be straight or branched. For example, an alkyl group may comprise propyl, which includes *n*-propyl and isopropyl, and butyl, which includes *n*-butyl, *sec*-butyl, isobutyl and *tert*-butyl. The term 'halo' as used herein signifies fluoro, chloro, bromo and iodo.

Compounds of formula I and intermediates in their preparation contain one or more chiral centres, and exist in different optically active forms. When compounds of formula I and intermediates in their preparation contain one chiral centre, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric

salts which may be separated, for example, by crystallisation; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When a compound of formula I contains more than one chiral centre it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to this skilled in the art, for example chromatography or crystallisation and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of formula I and mixtures thereof.

Certain compounds of formula I and their salts may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof. Certain compounds of formula I and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

Specific compounds of formula I are:-

N-{[1-(9-chloro-2,3-dihydrothieno[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]-methyl}pyridine-2-sulphonamide;

N-{[1-(2,3-dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl)piperid-4-yl]methyl}pyridine-2-sulphonamide;

4-acetamido-*N*-{[1-(2,3-dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl)piperid-4-yl]-methyl}benzenesulphonamide;

N-{[1-(2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}pyridine-2-sulphonamide

5 *N*-{[1-(2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}pyridine-3-sulphonamide

2,3-dichloro-*N*-{[1-(2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}benzenesulphonamide

10 *N*-{[1-(2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}-2,4-difluorobenzenesulphonamide

4-(acetamido)-*N*-{[1-(2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}benzenesulphonamide

15 and pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

Specific enantiomeric forms of compounds of formula I include:

20 (S)-*N*-{[1-(9-chloro-2,3-dihydrothieno[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}pyridine-2-sulphonamide;

25 (S)-*N*-{[1-(2,3-dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl)piperid-4-yl]methyl}pyridine-2-sulphonamide;

(S)-4-acetamido-*N*-{[1-(2,3-dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl)piperid-4-yl]methyl}benzenesulphonamide;

30 (S)-*N*-{[1-(2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}pyridine-2-sulphonamide

(S)-*N*-{[1-(2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}pyridine-3-sulphonamide

35 (S)-2,3-dichloro-*N*-{[1-(2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}benzenesulphonamide

40 (S)-*N*-{[1-(2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}-2,4-difluorobenzenesulphonamide

(S)-4-(acetamido)-*N*-{[1-(2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}benzenesulphonamide

45 and pharmaceutically acceptable salts thereof.

The present invention also includes pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I or a salt thereof together with a pharmaceutically acceptable diluent or carrier.

5 As used hereinafter, the term "active compound" denotes a compound of formula I or a salt thereof. In therapeutic use, the active compound may be administered orally, rectally, parenterally or topically, preferably orally. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for oral, rectal, parenteral or topical administration.

10 Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 0.1-99% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. Preferably the unit dosage of active ingredient is 1-500 mg. The excipients used in the preparation of these compositions are the excipients

15 known in the pharmacist's art.

 Compositions for oral administration are the preferred compositions of the invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, syrups and aqueous or oil suspensions. The excipients

20 used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared by mixing the active compound with an inert diluent such as calcium phosphate in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by known methods. The tablets may be formulated in a manner known to

25 those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by conventional means and, if

30 desired, provided with enteric coatings in a known manner. The tablets and capsules may conveniently each contain 1 to 500 mg of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethyl- cellulose, and oily suspensions

containing a compound of the present invention in a suitable vegetable oil, for example arachis oil.

5 The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example water) before ingestion. The granules may contain disintegrants (for example a pharmaceutically acceptable effervescent couple formed from an acid and a carbonate or bicarbonate salt) to facilitate dispersion in the liquid medium.

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 Compositions of the invention suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

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 Pharmaceutical compositions may also be administered parenterally (for example subcutaneously, intramuscularly, intradermally and/or intravenously [such as by injection and/or infusion]) in the known pharmaceutical dosage forms for parenteral administration (for example sterile suspensions in aqueous and/or oily media and/or sterile solutions in suitable solvents, preferably isotonic with the blood of the intended patient). Parenteral dosage forms may be sterilised (for example by micro-filtration and/or using suitable sterilising agents [such as ethylene oxide]). Optionally one or more of the following pharmaceutically acceptable adjuvants suitable for parenteral administration may be added to parenteral dosage forms: local anaesthetics, preservatives, buffering agents and/or mixtures thereof. Parenteral dosage forms may be stored in suitable sterile sealed containers (for example ampoules and/or vials) until use. To enhance stability during storage the parenteral dosage form may be frozen after filling the container and fluid (for example water) may be removed under reduced pressure.

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 Pharmaceutical compositions may be administered nasally in known pharmaceutical forms for such administration (for example sprays, aerosols, nebulised solutions and/or powders). Metered dose systems known to those skilled in the art (for example aerosols and/or inhalers) may be used.

Pharmaceutical compositions may be administered to the buccal cavity (for example sub-lingually) in known pharmaceutical forms for such administration (for example slow dissolving tablets, chewing gums, troches, lozenges, pastilles, gels, pastes, mouthwashes, rinses and/or powders).

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Compositions for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, for example paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream or ointment base. The amount of active compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The compounds of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as a suspension or solution in a pharmaceutically acceptable oil of the compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or ester or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

- 5 The present invention also comprises the use of a compound of formula I as a medicament.

 The compounds of formula I or salts thereof or pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I or a salt
10 thereof may be used to treat depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders, anorexia, cardiovascular and cerebrovascular
15 disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, and spasticity in human beings. Whilst the precise amount of active compound administered in such treatment will depend on a number of factors, for example the age of the patient, the severity of the condition and the past medical history and always lies within the sound discretion of
20 the administering physician, the amount of active compound administered per day is in the range 1 to 1000 mg preferably 5 to 500 mg given in single or divided doses at one or more times during the day.

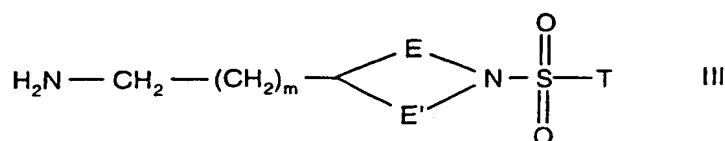
 A further aspect of the present invention provides the use of a compound of
25 formula I in the manufacture of a medicament for treating depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders and anorexia, cardiovascular
30 and cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, or spasticity in human beings.

The present invention also provides a method of treating depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive
 5 behaviour, panic attacks, social phobias, eating disorders and anorexia, cardiovascular and cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, or spasticity in human beings which comprises the administration of a therapeutically effective amount of a compound of formula I to a patient in need thereof.

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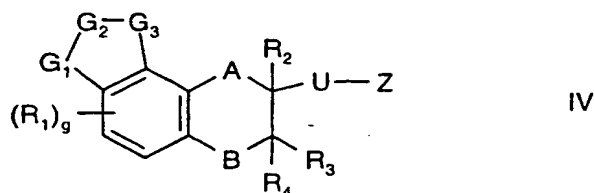
Processes for the preparation of compounds of formula I will now be described. These processes form a further aspect of the present invention. The processes are preferably carried out at atmospheric pressure, at a temperature in the range 0-200°C, preferably in the range 20-150°C. The substituents are as defined for formula I above
 15 unless otherwise stated.

Compounds of formula I in which Q is a group of formula IIa in which R_5 is H, and V is $(CH_2)_n$ wherein n is 1, 2 or 3 may be prepared by reaction of a compound of formula III



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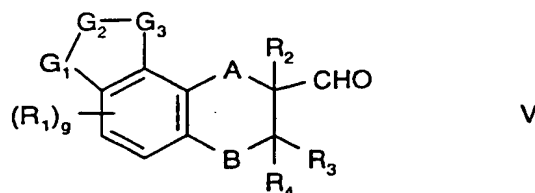
in which m is 0, 1 or 2, with a compound of formula IV



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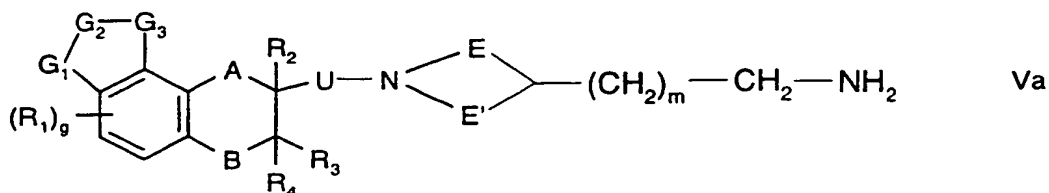
in which Z is a leaving group, for example toluene-4-sulphonyloxy, optionally in the presence of a suitable solvent, for example acetonitrile, optionally in the presence of a base, for example potassium carbonate, and optionally in the presence of a catalyst, for example potassium iodide.

Compounds of formula I in which U is methylene and Q is a group of formula IIa in which R_5 is H, and V is $(CH_2)_n$ wherein n is 1, 2 or 3, and R'' and R''' are other than formyl may be prepared by reaction of a compound of formula V



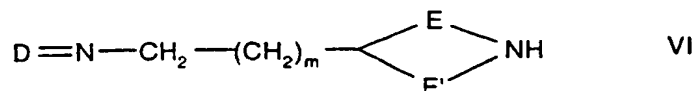
- 5 with a compound of formula III, followed by reduction of the intermediate imine with a suitable reducing agent, for example sodium borohydride.

Compounds of formula I in which Q represents a group of formula IIc in which R_6 is H and V is $(CH_2)_n$ wherein n is 1, 2 or 3 may be prepared by reacting a compound of
10 formula Va



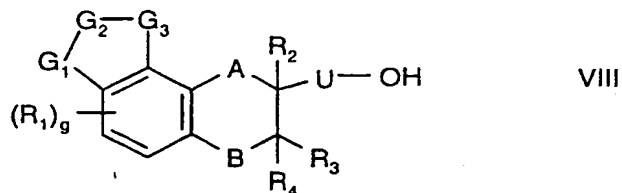
- in which m is 0, 1 or 2 with a compound of formula $X-SO_2-T$ in which X is a leaving group, for example halo or hydroxy, in the presence of a base, for example triethylamine, in a suitable solvent such as dichloromethane.
15

Compounds of formula III may be prepared by reaction of a compound of formula VI



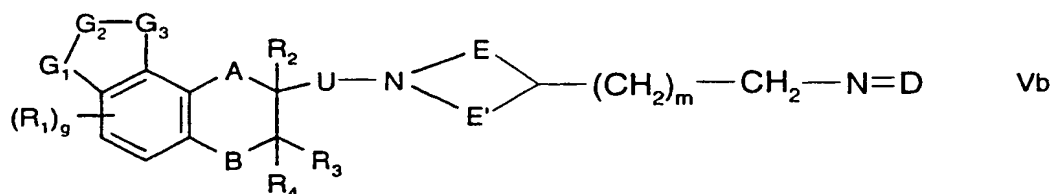
- 20 in which D is a protecting group, for example 5-bromo-2-hydroxybenzylidene, and m is 0, 1 or 2, with a sulfonylating agent of formula $X-SO_2-T$ in which X is a leaving group, for example halo or hydroxy, in the presence of a base, for example triethylamine, in a suitable solvent such as dichloromethane, followed by removal of the protecting group, for example by acid-catalysed hydrolysis.

Compounds of formula IV in which Z is toluene-4-sulphonyloxy may be prepared by reaction of a compound of formula VIII



with toluene-4-sulphonyl chloride, optionally in the presence of a base, for example pyridine.

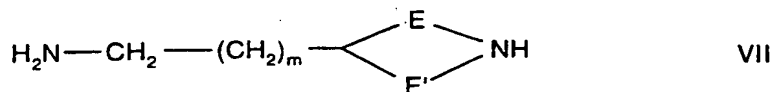
Compounds of formula Va may be prepared by deprotecting a compound of formula Vb



in which D is a protecting group, for example by acid catalysed hydrolysis.

Compounds of formula Vb may be prepared by reacting a compound of formula IV with a compound of formula VI optionally in the presence of a suitable solvent, for example acetonitrile, optionally in the presence of a base, for example potassium carbonate, and optionally in the presence of a catalyst, for example potassium iodide.

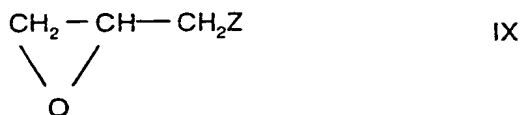
Compounds of formula VI may be prepared by reaction of a compound of formula VII



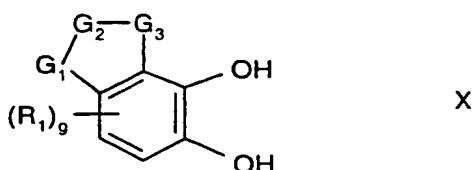
in which m is 0, 1 or 2, with a protecting reagent, for example 5-bromo-2-hydroxybenzaldehyde.

Compounds of formula VIII in which A and B are both -O-, R₂, R₃ and R₄ are all H, and U is methylene may be prepared by reaction of a compound of formula IX

15

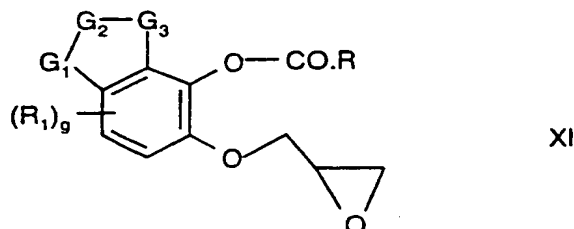


in which Z is a leaving group, for example chloro or toluene-4-sulphonyloxy, with a compound of formula X



- 5 in a suitable solvent, for example water or dimethylformamide in the presence of a base, for example sodium hydroxide. When the appropriate enantiomerically pure form of a compound of formula IX, for example (*R*)-glycidyl 4-toluenesulphonate, is used, the single (*S*)-enantiomer of a compound of formula VIII can be prepared.

- 10 Compounds of formula VIII in which A and B are both -O-, U is methylene, and R₂, R₃ and R₄ are all H, may also be prepared by cyclisation of a compound of formula XI



- 15 in which R is H or an alkyl group containing 1 to 4 carbon atoms, using a base, for example potassium carbonate.

Compounds of formula VIII in which R'' is H or CO₂Et may be prepared by cyclisation of the appropriate compound of formula XI in the presence of potassium carbonate.

20

Compounds of formula VIII in which R'' is CO₂H may be prepared by hydrolysis of the corresponding compound of formula VIII in which R'' is CO₂Et.

Compounds of formula VIII in which R'' is H may also be prepared by decarboxylation of the corresponding compound of formula VIII in which R'' is CO₂H.

- 5 Compounds of formula VIII in which R'' is CONH₂ may be prepared by amination of the corresponding compound of formula VIII in which R'' is CO₂Et.

Compounds of formula VIII in which R'' is CONMe₂ may be prepared by amination of the corresponding compound of formula VIII in which R'' is CO₂Et.

10

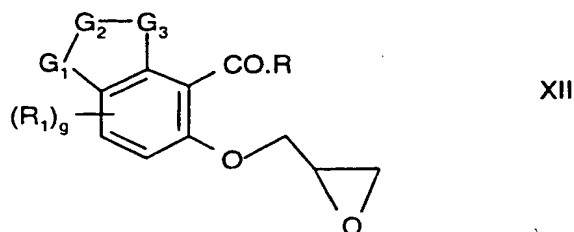
Compounds of formula VIII in which R'' is CHO may be prepared by reduction of the corresponding compound of formula VIII in which R'' is CO₂Et.

- 15 Compounds of formula VIII in which R'' is COMe may be prepared by reaction of the corresponding compound of formula VIII in which R'' is CO₂H with methyl lithium.

Compounds of formula VIII in which R'' is CN may be prepared by dehydration of the corresponding compound of formula VIII in which R'' is CONH₂.

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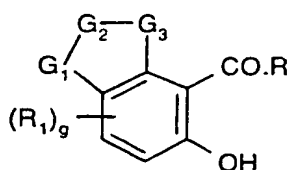
Compounds of formula XI may be prepared by oxidation of compounds of formula XII



- 25 in which R is H or an alkyl group containing 1 to 4 carbon atoms, with a peroxyacid, for example 3-chloroperoxybenzoic acid.

Compounds of formula XII may be prepared by alkylating compounds of formula XIII

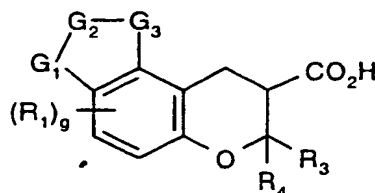
17



XIII

in which R is H or an alkyl group containing 1 to 4 carbon atoms, with compounds of formula IX, in which Z is a leaving group, for example chloro or toluene-4-sulphonyloxy, in a suitable solvent, for example dimethylformamide, in the presence of a base, for example potassium carbonate. When the appropriate enantiomerically pure form of a compound of formula IX, for example (*R*)-glycidyl 4-toluenesulphonate, is used, the single (*S*)-enantiomer of a compound of formula VIII can be prepared.

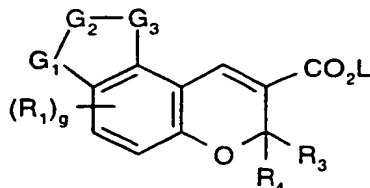
Compounds of formula VIII in which A and U are methylene, B is -O-, R₂ is H and R'' and R''' are H or cyano, may be prepared by reduction of a compound of formula XIV



XIV

with a reducing agent, for example borane-dimethyl sulphide complex.

Compounds of formula XIV may be prepared by reduction of a compound of formula XV



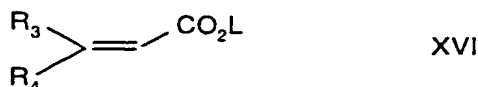
XV

in which L is H with a reducing agent, for example hydrogen in the presence of a palladium-on-carbon catalyst.

20

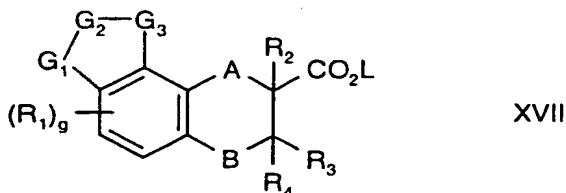
Compounds of formula XV in which L is H may be prepared by acid or base-catalysed hydrolysis of a compound of formula XV in which L is an alkyl group containing 1 to 6 carbon atoms.

Compounds of formula XV in which L is an alkyl group may be prepared by reaction of a compound of formula XIII in which R is H with a compound of formula XVI



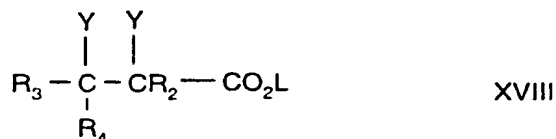
- 5 in which L is an alkyl group containing 1 to 6 carbon atoms, in the presence of a base, for example 1,4-diazabicyclo[2.2.2]octane (DABCO).

- 10 Compounds of formula V may be prepared by oxidation of a compound of formula VIII in which U is methylene with a suitable oxidising agent, for example pyridinium chlorochromate or by reduction of a compound of formula XVII



with a suitable reducing agent, for example sodium bis(2-methoxyethoxy)aluminium hydride in a solvent, for example toluene.

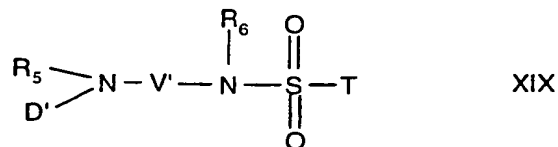
- 15 Compounds of formula XVII in which A and B are both -O- may be prepared by reaction of a compound of formula XVIII



- 20 in which Y is a leaving group, for example bromo, and L is an alkyl group containing 1 to 6 carbon atoms with a compound of formula X, in the presence of a base, for example potassium carbonate.

- 25 Compounds of formula XVII in which A is methylene, B is -O-, R₂ is H and L is an alkyl group containing 1 to 6 carbon atoms may be prepared by reduction of a compound of formula XV in which L is an alkyl group containing 1 to 6 carbon atoms, with a suitable reducing agent, for example hydrogen in the presence of a palladium-on-carbon catalyst.

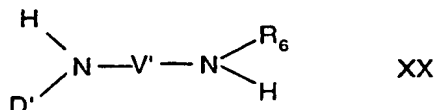
Compounds of formula I in which Q is a group of formula IIb may be prepared by reaction of a compound of formula IV in which Z is a leaving group, for example toluene-4-sulphonyloxy, with a compound of formula XIX



- 5 in which D' is H, optionally in the presence of a base, for example potassium carbonate, and optionally in a solvent, for example acetonitrile.

- 10 Compounds of formula XIX in which D' is H may be prepared by deprotection of a compound of formula XIX in which D' is a protecting group, for example *tert*-butoxycarbonyl, for example by hydrolysis in the presence of an acid, for example trifluoroacetic acid.

Compounds of formula XIX in which D' is a protecting group may be prepared by reaction of a compound of formula XX

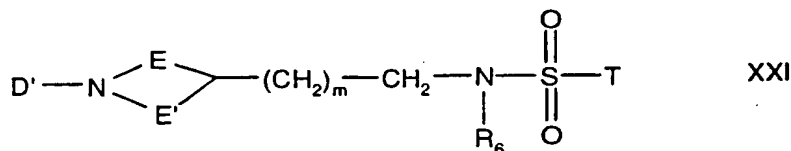


15

in which D' is a protecting group, for example *tert*-butoxycarbonyl, with a compound of formula X-SO₂-T in which X is a leaving group, for example halo, alkoxy, hydroxy or alkoxycarbonyloxy, in the presence of a base, for example triethylamine, in a suitable solvent such as dichloromethane.

20

Compounds of formula I in which Q is a group of formula IIc in which V is (CH₂)_n wherein n is 1, 2, or 3 may be prepared by reaction of a compound of formula XXI

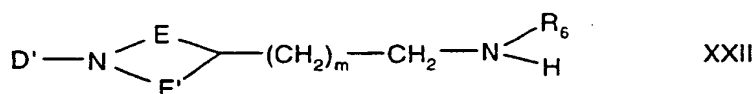


- 25 in which D' is H and m is 0, 1 or 2, with a compound of formula IV in which Z is a leaving group, for example toluene-4-sulphonyloxy, optionally in the presence of a base, for example potassium carbonate, and optionally in a solvent, for example acetonitrile.

Compounds of formula XXI in which D' is H may be prepared by deprotection of a compound of formula XXI in which D' is a protecting group, for example *tert*-butoxycarbonyl, for example by hydrolysis in the presence of an acid, for example

5 trifluoroacetic acid.

Compounds of formula XXI in which D' is a protecting group may be prepared by reaction of a compound of formula XXII



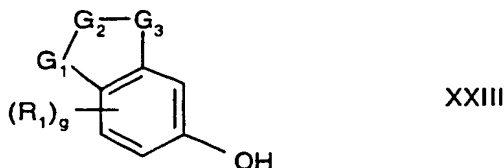
10 in which D' is a protecting group, for example *tert*-butoxycarbonyl, and m is 0, 1 or 2, with a compound of formula X-SO₂-T in which X is a leaving group, for example halo or hydroxy, in the presence of a base, for example triethylamine, in a suitable solvent such as dichloromethane.

15 Compounds of formula IV in which G₁-G₂-G₃ are -NH-CH=CH- are known (J.Med.Chem.,1992,35, pg 3058).

Compounds of formula I in which R₅ is an alkyl group and R'' and R''' are other than formyl may be prepared by alkylation of a compound of formula I in which R₅ is H

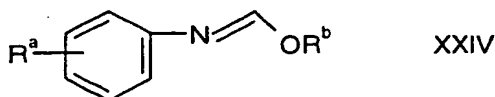
20 with for example formaldehyde and formic acid, or an aldehyde and a reducing agent such as sodium cyanoborohydride.

Compounds of formula XIII in which R is H may be prepared by reaction of a compound of formula XXIII



25

with an N-arylformimidate ester of formula XXIV



in which R^a is H, an alkyl group containing 1 to 3 carbon atoms, an alkoxy group containing 1 to 3 carbon atoms, or halo, and R^b is an alkyl group containing 1 to 3 carbon atoms, for example ethyl N-(4-methoxyphenyl)formimidate, followed by hydrolysis of the intermediate imine in the presence of an acid. Compounds of formula
5 IV in which G₁-G₂-G₃ are other than -NH-CH=CH- may be prepared by methods analogous to that described above.

The ability of compounds of formula I to interact with 5-hydroxytryptamine (5-HT) receptors has been demonstrated by the following test which determines the ability of
10 the compounds to inhibit tritiated ligand binding to 5-HT receptors in vitro and in particular to 5-HT_{1A} receptors.

Hippocampal tissue from the brains of male Charles River CD rats weighing between 150-250 g were homogenised in ice-cold 50 mM Tris-HCl buffer (pH 7.7) when
15 measured at 25°C, 1:40 w/v) and centrifuged at 30,000 g at 4°C for 10 minutes. The pellet was rehomogenised in the same buffer, incubated at 37°C for 10 minutes and centrifuged at 30,000 g at 4°C for 10 minutes. The final pellet was resuspended in 50 mM Tris-HCl buffer (pH 7.7) containing 4 mM CaCl₂, 0.1% L-ascorbic acid and 10 µM pargyline hydrochloride (equivalent to 6.25 mg wet weight of tissue/ml) and used
20 immediately in the binding assay. Aliquots (400 µl; equivalent to 2.5 mg wet weight of tissue/tube) of this suspension were added to tubes containing the ligand (50 µl; 2 nM) and distilled water (50 µl; total binding) or 5-HT (50 µl; 10 µM; non-specific binding) or test compound (50 µl; at a single concentration of 10⁻⁶ M or at 10 concentrations ranging from 10⁻¹¹-10⁻³ M). The ligand was [³H]8-hydroxy-2-(dipropylamino)tetralin ([³H]8-OH-
25 DPAT) and the mixture was incubated at 25°C for 30 minutes before the incubation was terminated by rapid filtration.

The filters were washed with ice-cold Tris-HCl buffer and dried. The filters were punched out into vials, scintillation fluid added and radioactivity determined by liquid
30 scintillation counting. The percentage displacement of specific binding of the tritiated ligand was calculated for the single concentration (10⁻⁶ M) of test compound. Displacement curves were then produced for those compounds which displaced ≥50% of specific binding of the tritiated ligand at 10⁻⁶ M using a range of concentrations of the

compound. The concentration which gave 50% inhibition of specific binding (IC_{50}) was obtained from the curve. The inhibition coefficient K_i was then calculated using the formula

5

$$K_i = \frac{IC_{50}}{1 + ([\text{ligand}]/K_D)}$$

- 10 in which $[\text{ligand}]$ is the concentration of the tritiated ligand used and K_D is the equilibrium dissociation constant for the ligand.

The ability of compounds of formula I to interact with dopamine receptors has been demonstrated by the following test which determines the ability of the compounds
15 to inhibit tritiated ligand binding to dopamine receptors in vitro and in particular to the D_2 -like dopamine receptors.

Striatal tissue from the brains of male Charles River CD rats weighing between 140-250g were homogenised in ice-cold 50 mM Tris-HCl buffer (pH 7.7 when measured
20 at 25°C) and centrifuged at 40,000 g for 10 minutes. The pellet was resuspended in Tris salts buffer (50 mM Tris-HCl buffer containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$ and 1 mM $MgCl_2$ with the addition of 6 mM ascorbic acid; pH 7.7 when measured at 25°C), and again centrifuged at 40,000 g for 10 minutes. The final pellet was stored at -80°C. Before each test the pellet was resuspended in Tris salts buffer (equivalent to
25 2 mg wet weight of tissue/ml). Aliquots (720 μ l; equivalent to 1.44 mg wet weight of tissue/tube) of this suspension were then added to tubes containing the ligand (40 μ l; 1 nM) and Tris salts buffer (40 μ l; total binding) or spiroperidol (40 μ l; 10 nM; non-specific binding) or test compound (40 μ l; at a single concentration of 10^{-6} M or at 6 concentrations ranging from 10^{-11} - 10^{-4} M). The ligand was tritiated (*S*)-sulpiride and the
30 mixture was incubated at 4°C for 40 minutes before the incubation was terminated by rapid filtration.

The filters were washed with ice-cold Tris-HCl buffer and dried. The filters were punched out in to vials, scintillation fluid added and were left for about 20 hours before
35 being counted by scintillation spectrophotometry. The percentage displacement of

specific binding of the tritiated ligand was calculated for the single concentration (10^{-6} M) of test compound. Displacement curves were then produced over a range of concentrations for those compounds which displaced $\geq 50\%$ of specific binding of the tritiated ligand at 10^{-6} M. The concentration which gave a 50% inhibition of specific binding (IC₅₀) was obtained from the curve. The inhibition coefficient K_i was then calculated using the formula

$$K_i = \frac{IC_{50}}{1 + ([\text{ligand}]/K_D)}$$

in which [ligand] is the concentration of the tritiated ligand used and K_D is the equilibrium dissociation constant for the ligand.

The K_i values obtained in the above tests for 5-HT_{1A} and D₂-like binding for each of the final products of the Examples hereinafter are given in Table 1 below.

TABLE 1

Example Number	K _i (nM) value for	
	5-HT _{1A}	D ₂ -like
1	98%	106%
2	99%	105%
3	97%	105%

The % figures in Table 1 are for % displacement at 10^{-6} M.

The invention is illustrated by the following Examples which are given by way of example only. The final product of each Example was characterised by one or more of the following procedures: gas-liquid chromatography; high performance liquid chromatography; elemental analysis, nuclear magnetic resonance spectroscopy and infrared spectroscopy.

Example 1

A stirred solution of ethyl 3-chloro-5-methoxybenzo[*b*]thiophene-2-carboxylate (20.0 g) in dichloromethane (80 ml) at -20 °C under an atmosphere of nitrogen was treated with boron tribromide (1M solution in dichloromethane; 90 ml) and the solution allowed to warm up to room temperature slowly. After 2 hours the mixture was carefully poured into ethanol (400 ml) and left to stand for 10 minutes. The solvent was evaporated under reduced pressure and the residue dissolved in ethyl acetate (500 ml). The resulting solution was washed with water (300 ml), dried over sodium sulphate and the solvent evaporated under reduced pressure to give ethyl 3-chloro-5-hydroxybenzo[*b*]thiophene-2-carboxylate (18.68 g) as an off-white solid; m.p. 160-161°C.

A round bottomed flask containing a mixture of the product from the previous reaction (6.04 g) and ethyl *N*-(4-methoxyphenyl)formimidate (4.50 g) was submerged rapidly in an oil bath pre-heated to 160 °C, and the mixture stirred at 160-80 °C for 4 hours, the ethanol produced in the reaction being removed by distillation. More of the formimidate (0.80 g) was then added and the mixture heated at 180-90 °C for a further 1 hour. The cooled mixture was then treated with boiling methanol (100 ml) and the resulting light brown solid collected by filtration, washed with methanol (100 ml) and dried to give ethyl 3-chloro-5-hydroxy-4-[*N*-(4-methoxyphenyl)iminomethyl]benzo[*b*]thiophene-2-carboxylate (4.03 g); m.p. 162-163°C.

A stirred mixture of the product from the previous reaction (3.82 g) and hydrochloric acid (4M; 130 ml) was heated at 50-60 °C for 4 hours and then left to stand at room temperature overnight. The mixture was then heated at 60-70 °C for 3 hours. The cooled mixture was poured into water (350 ml) and extracted with ethyl acetate (2x250 ml). The combined organic extracts were washed with water (200 ml), dried over sodium sulphate and evaporated under reduced pressure to give ethyl 3-chloro-4-formyl-5-hydroxybenzo[*b*]thiophene-2-carboxylate (2.80 g) as a pale-green solid; m.p. 128-130°C.

Potassium carbonate (2.62 g) was added to a stirred solution of ethyl 3-chloro-4-formyl-5-hydroxybenzo[*b*]thiophene-2-carboxylate (4.90 g, prepared as described above) in dry dimethylformamide (50 ml) and then a solution of (*R*)-glycidyl tosylate (4.12 g) in dry dimethyl formamide (50 ml) was added slowly. The mixture was then stirred at 60 °C for 3 hours, cooled and poured into water (1200 ml). The resulting pale-green solid was collected by filtration, washed with water (200 ml) and dried to give ethyl (*R*)-3-chloro-5-(2,3-epoxypropoxy)-4-formylbenzo[*b*]thiophene-2-carboxylate (5.15g).

A stirred solution of the product from the previous reaction (1.0 g) in dichloromethane (20 ml) was treated with 3-chloroperoxybenzoic acid (85%; 0.75 g) and the mixture cooled to 0 °C. A solution of trifluoroacetic acid (0.335 g) in dichloromethane (5 ml) was then added and the solution stirred at 0 °C for 5 minutes and then at room temperature for 1 hour. The mixture was poured into saturated aqueous sodium bisulphite solution (100 ml) and extracted with dichloromethane (2x100 ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (2x150 ml), dried over sodium sulphate and evaporated under reduced pressure to give a brown oil. Purification by flash chromatography on silica using a 1:1 mixture of petroleum ether (b.p. 60-80 °C) and ethyl acetate as eluant gave ethyl (*R*)-3-chloro-5-(2,3-epoxypropoxy)-4-formyloxybenzo[*b*]thiophene-2-carboxylate (0.52 g) as a pale-yellow solid.

Saturated aqueous potassium carbonate solution (20 ml) was added to a stirred solution of ethyl (*R*)-3-chloro-5-(2,3-epoxypropoxy)-4-formyloxybenzo[*b*]thiophene-2-carboxylate (1.85 g, prepared as described above) in tetrahydrofuran (20 ml) and the mixture stirred for 24 hours at room temperature. The reaction mixture was poured into water (200 ml) and extracted with ethyl acetate (2x 100 ml). The combined extracts were dried over sodium sulphate and evaporated under reduced pressure to give a yellow solid. Purification by flash chromatography on silica using a 1:1 mixture of petroleum ether (b.p. 60-80 °C) and ethyl acetate as eluant gave ethyl (*S*)-9-chloro-2,3-dihydro-2-(hydroxymethyl)thieno[3,2-*f*][1,4]-benzodioxin-8-carboxylate (1.44 g) as a pale-yellow solid; m.p. 165-166°C.

A stirred solution of the product from the previous reaction (1.30 g) in methanol (20 ml) was treated with a solution of lithium hydroxide monohydrate (0.17 g) in water (10 ml) and the mixture heated at 60°C for 1 hour. The solution was evaporated under reduced pressure to remove methanol and then diluted with water (50 ml). The aqueous solution was acidified with hydrochloric acid (2 M) and the resulting suspension collected by filtration, washed with water and dried to give (S)-9-chloro-2,3-dihydro-2-(hydroxymethyl)thieno[3,2-f][1,4]benzodioxin-8-carboxylic acid (1.15 g) as an off-white solid, m.p. 236-7°C.

10 A round bottomed flask containing a mixture of the product from the previous reaction (0.80 g), copper powder (0.17 g) and quinoline (10 ml) was rapidly submerged in an oil bath pre-heated to 190°C, and the mixture heated with stirring at this temperature for 30 minutes. The mixture was cooled to room temperature and poured into hydrochloric acid (2M; 300 ml). The mixture was
15 extracted with ethyl acetate (2x150 ml) and the combined extracts washed with hydrochloric acid (2M; 150 ml), water (150 ml), then dried over sodium sulphate and evaporated under reduced pressure to give a dark brown oil (0.781 g). Purification by flash chromatography on silica using a 3:7 mixture of ethyl acetate and petroleum ether (b.p. 60-80°C) as eluant gave (S)-9-chloro-2,3-dihydro-2-
20 (hydroxymethyl)thieno[3,2-f][1,4]benzodioxin (0.58 g) as a fawn solid, m.p. 92-3°C.

A stirred solution of the product from the previous reaction (0.49 g) in dichloromethane (20 ml) was treated with 4-(dimethylamino)pyridine (0.26 g). 4-Toluenesulphonyl chloride (0.40 g) was then added and the resulting solution stirred
25 for 24 hours at room temperature. The reaction mixture was poured into water (100 ml) and extracted with dichloromethane (150 ml). The organic extract was washed successively with saturated copper sulphate solution (2x100 ml), water (100 ml), dried over sodium sulphate and evaporated under reduced pressure to give (S)-9-chloro-2,3-dihydrothieno[3,2-f][1,4]benzodioxin-2-ylmethyl 4-toluenesulphonate
30 (0.70 g) as a white solid, m.p. 169-70°C.

A stirred solution of *N*-[(1-*tert*-butoxycarbonylpiperid-4-yl)methyl]pyridine-2-sulphonamide (0.20 g) in dichloromethane (10 ml) was treated with trifluoroacetic

acid (2 ml) and the mixture stirred at room temperature for 2 hours. The mixture was evaporated under reduced pressure and the oily residue dissolved in dry acetonitrile (20 ml). Potassium carbonate (3.0 g) and a solution of the product from the previous reaction (0.095 g) in dry acetonitrile (10 ml) was then added and the mixture heated under reflux with stirring for 24 hours. The cooled reaction mixture was filtered and the solvent removed under reduced pressure. The residue was redissolved in dichloromethane (200 ml) and washed with water (100 ml). The organic solution was dried over sodium sulphate and evaporated under reduced pressure to give a yellow oil (0.15 g). Purification by flash column chromatography on silica using a 95:5 mixture of dichloromethane and methanol as eluant gave (*S*)-*N*-{[1-(9-chloro-2,3-dihydrothieno[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}pyridine-2-sulphonamide (0.042 g) as a white solid.

Example 2

A stirred solution of *N*-[(1-*tert*-butoxycarbonylpiperid-4-yl)methyl]pyridine-2-sulphonamide (1.20 g) in dichloromethane (80 ml) was treated with trifluoroacetic acid (6 ml) and the mixture stirred at room temperature for 2 hours. The mixture was evaporated under reduced pressure and the oily residue dissolved in dry acetonitrile (50 ml). Potassium carbonate (6.0 g) and a solution of (*S*)-2,3-dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl 4-toluenesulphonate (1.28 g) in dry acetonitrile (20 ml) was then added and the mixture heated under reflux with stirring for 24 hours. The cooled reaction mixture was filtered and the solid washed with dichloromethane (100 ml). The filtrate was evaporated under reduced pressure and the residue purified by flash chromatography on silica using a 95:5 mixture of dichloromethane and methanol as eluant to give (*S*)-*N*-{[1-(2,3-dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl)piperid-4-yl]methyl}pyridine-2-sulphonamide 0.075 dichloromethane solvate (0.58 g) as an off-white solid, m.p. 86-88°C, $[\alpha]_D -39.3$ ($c=0.217$, MeOH).

Example 3

A stirred solution of 4-(aminomethyl)-1-(*tert*-butoxycarbonyl)piperidine (5.20 g) in dichloromethane (100 ml) was treated with triethylamine (5.31 g) and then 4-acetamidobenzenesulphonyl chloride (6.07 g) was added in small portions. The

mixture was stirred at room temperature for 4 hours and then left to stand for 72 hours. The mixture was poured into water (200 ml) and extracted with dichloromethane (150 ml). The organic solution was washed with hydrochloric acid (1M; 100 ml) which led to precipitation of a pale-yellow solid. The solid was collected
5 by filtration, dissolved in industrial methylated spirit (300 ml), dried over sodium sulphate and evaporated under reduced pressure to give *N*-{[4-acetamido-1-(*tert*-butoxycarbonyl)-4-piperidyl]methyl}benzenesulphonamide (3.72 g) as a pale-yellow solid, m.p. 226-7°C.

10 A stirred solution of the product from the previous reaction (1.40 g) in dichloromethane (30 ml) was treated with trifluoroacetic acid (4 ml) and the solution stirred at room temperature for 2 hours. The mixture was then evaporated under reduced pressure and re-dissolved in dry acetonitrile (50 ml). Potassium carbonate (7.0 g) and a solution of (S)-2,3-dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl 4-
15 toluenesulphonate (1.20 g) in dry acetonitrile (20 ml) was then added and the mixture heated under reflux with stirring for 24 hours. The cooled mixture was filtered and the solid washed with dichloromethane (100 ml). The filtrate was then evaporated under reduced pressure and the residue purified by flash column chromatography on silica using a 9:1 mixture of dichloromethane and methanol as
20 eluant to give a pale-yellow solid which was triturated with diethyl ether to give (S)-4-acetamido-*N*-{[1-(2,3-dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl)piperid-4-yl]-methyl} benzenesulphonamide 0.75 hydrate (0.76 g) as an off-white solid, m.p. 133-4°C, $[\alpha]_D -33.5^\circ$ ($c = 0.257$, EtOH).

25 Example 4-8

Potassium carbonate (2.85 g), and a solution of (*R*)-glycidyl 4-toluenesulphonate (4.50 g) in dry dimethylformamide (10 ml) were added to a stirred solution of 5-hydroxybenzo[*b*]furan-4-carboxaldehyde (3.04 g) in dry
30 dimethylformamide (30 ml). The mixture was heated at 60 °C for 2 hours and then poured into water (500 ml). The mixture was extracted with dichloromethane (3x300 ml) and the combined extracts were washed with water (8x200 ml), dried over sodium sulphate and evaporated under reduced pressure to give a red oil. Purification by flash column chromatography on silica eluting with a 3:7 mixture of

ethyl acetate and petroleum ether (b.p. 40-60 °C) gave (*R*)-5-[2-(2,3-epoxypropoxy)]benzo[*b*]furan-4-carboxaldehyde (3.11 g) as a yellow solid m.p. 64-5 °C.

- 5 3-Chloroperoxybenzoic acid (85%; 3.88 g) and a solution of trifluoroacetic acid (1.61 g) in dichloromethane (5 ml) were added to a stirred solution of the product from the previous reaction (3.08 g) in dichloromethane (40 ml). The mixture was stirred at room temperature for 30 minutes and poured into saturated aqueous sodium bisulphite (200 ml) then extracted with dichloromethane (2x150 ml). The
- 10 combined extracts were washed with saturated aqueous sodium bicarbonate (3x150 ml), dried over sodium sulphate and evaporated under reduced pressure to give (*R*)-5-[2-(2,3-epoxypropoxy)]benzo[*b*]furan-5-yl formate (3.10 g) as a red oil.

- Saturated aqueous potassium carbonate (15 ml) was added to a stirred
- 15 solution of the product from the previous reaction (3.09 g) in tetrahydrofuran (30 ml) and the mixture stirred vigorously at room temperature for 72 hours. The mixture was poured into water (200 ml) and extracted with ethyl acetate (2x150 ml). The combined extracts were dried over sodium sulphate and evaporated under reduced pressure to give an orange oil. Purification by flash column chromatography on
- 20 silica eluting with a 2:3 mixture of ethyl acetate and petroleum ether (b.p. 60-80 °C) gave (*S*)-2,3-dihydro-2-(hydroxymethyl)furo[3,2-*f*][1,4]benzodioxin (1.90 g) as a pale yellow oil.

- 4-Toluenesulphonyl chloride (1.89 g) was added to a stirred solution of the
- 25 product from the previous reaction (1.86 g) in dichloromethane (40 ml). 4-Dimethylaminopyridine (1.21 g) was then added and the resulting solution stirred at room temperature for 18 hours. The mixture was diluted with dichloromethane (200 ml) and washed successively with water (100 ml), saturated aqueous copper sulphate solution (2x100 ml) and water (100 ml). The organic solution was then
- 30 dried over sodium sulphate and evaporated under reduced pressure to give (*S*)-2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-ylmethyl 4-toluenesulphonate (3.01 g) as a colourless oil.

In a similar manner to Example 3 (S)-2,3-dihydrofuro[3,2-f]benzodioxin-2-ylmethyl 4-toluenesulphonate is reacted with an appropriate compound of formula III to give

5 Example 4

(S)-N-[[1-(2,3-dihydrofuro[3,2-f][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl]pyridine-2-sulphonamide

Example 5

10 (S)-N-[[1-(2,3-dihydrofuro[3,2-f][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl]pyridine-3-sulphonamide

Example 6

15 (S)-2,3-dichloro-N-[[1-(2,3-dihydrofuro[3,2-f][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl]benzenesulphonamide

Example 7

20 (S)-N-[[1-(2,3-dihydrofuro[3,2-f][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl]-2,4-difluorobenzenesulphonamide

Example 8

(S)-4-(acetamido)-N-[[1-(2,3-dihydrofuro[3,2-f][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl]benzenesulphonamide.

25 Pharmaceutical Examples

30 The use of compounds of the present invention in the manufacture of pharmaceutical compositions is illustrated by the following description. In this description the term "active compound" denotes any compound of the invention but particularly any compound which is the final product of one of the preceding Examples.

a) Capsules

35 In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing a unit dose or part of a unit dose of active compound.

b) Tablets

Tablets are prepared from the following ingredients.

		<u>Parts by weight</u>
5	Active compound	10
	Lactose	190
	Maize starch	22
	Polyvinylpyrrolidone	10
	Magnesium stearate	3
10		

The active compound, the lactose and some of the starch are de-aggregated, blended and the resulting mixture is granulated with a solution of the polyvinylpyrrolidone in ethanol. The dry granulate is blended with the magnesium stearate and the rest of the starch. The mixture is then compressed in a tableting machine to give 15 tablets each containing a unit dose or a part of a unit dose of active compound.

Enteric coated tablets

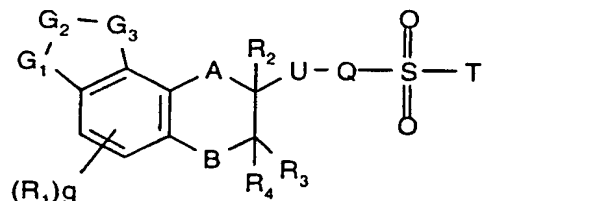
Tablets are prepared by the method described in (b) above. The tablets are 20 enteric coated in a conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

d) Suppositories

25 In the preparation of suppositories, 100 parts by weight of active compound is incorporated in 1300 parts by weight of triglyceride suppository base and the mixture formed into suppositories each containing a therapeutically effective amount of active ingredient.

Claims

1) Compounds of formula I



5 including enantiomers and pharmaceutically acceptable salts thereof in which

A is methylene or -O-;

B is methylene or -O-;

10

G_1 - G_2 - G_3 represent -N(R')-C(R'')=N-, -N=C(R'')-N(R')-, -N(R')-C(R'')=C(R''')-,
 -C(R''')=C(R'')-N(R')-, -N(R')-N=C(R'')-, -C(R'')=N-N(R')-, -N(R')-N=N-, -N=N-N(R')-,
 -N=C(R'')-O-, -N=C(R'')-S-, -O-C(R'')=N-, -S-C(R'')=N-, -O-N=C(R'')-, -S-N=C(R'')-,
 -C(R'')=N-O-, -C(R'')=N-S-, -S-C(R'')=C(R''')-, -C(R'')=C(R''')-S-, -O-C(R'')=C(R''')-,
 15 C(R'')=C(R''')-O- or -O-C(R'')(R')-O-;

R' is H or an alkyl group containing 1 to 3 carbon atoms;

R'' and R''', which are the same or different, are H; halo; an alkyl group
 20 containing 1 to 3 carbon atoms optionally substituted by one or more halo; carboxy; an
 alkanoyl group containing 1 to 6 carbon atoms; an alkoxycarbonyl group in which the
 alkoxy group contains 1 to 3 carbon atoms; formyl; cyano; or a carbamoyl group or
 carbamoylmethyl group each optionally *N*-substituted by one or two alkyl groups, which
 may be the same or different, each containing 1 to 3 carbon atoms;

25

g is 0, 1 or 2;

R₁ represents an alkyl group containing 1 to 3 carbon atoms optionally substituted by
 one or more halo; an alkoxy group containing 1 to 3 carbon atoms optionally substituted
 30 by one or more halo; halo; or an alkylthio group containing 1 to 3 carbon atoms

optionally substituted by one or more halo; the substituents represented by R_1 being the same or different when g is 2;

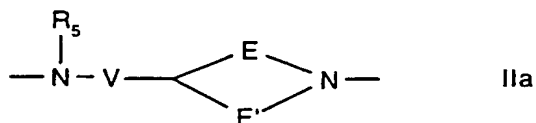
R_2 is H or an alkyl group containing 1 to 3 carbon atoms;

5

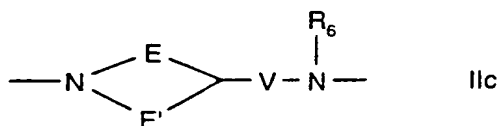
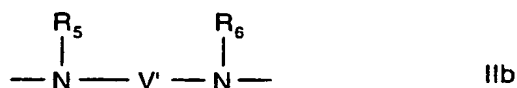
R_3 and R_4 , which are the same or different, are H, or an alkyl group containing 1 to 3 carbon atoms;

10 U is an alkylene chain containing 1 to 3 carbon atoms, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

Q represents a divalent group of formula IIa, IIb or IIc



15



20 in which V is $(CH_2)_n$, wherein n is 0, 1, 2 or 3, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

V' is an alkylene chain containing 2 to 6 carbon atoms, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

25 E is an alkylene chain containing 0 to 2 carbon atoms and E' is an alkylene chain containing 1 to 4 carbon atoms provided that the total number of carbon atoms in E and E' amounts to 3 or 4;

R₅ and R₆, which may be the same or different, are H or an alkyl group containing 1 to 4 carbon atoms; and

T represents phenyl, 1- or 2-naphthyl, 1-naphth[2,1-*d*][1,2,3]oxadiazolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-thienyl, 2- or 3-furyl, 2-, 3- or 7-benzo[*b*]furanyl, 2,3-dihydro-7-benzo[*b*]furanyl, 2-, 3- or 7-benzo[*b*]thiophenyl, 3-, 4- or 5-pyrazolyl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-2-yl, 5-tetrazolyl, 2-, 3- or 4-quinolyl, 2- or 4-quinazolinyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isothiazolyl or 2-, 4- or 5-thiazolyl each of which may be optionally substituted by one or more substituents selected from a) halo, b) an alkyl group containing 1 to 4 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g) hydroxymethyl, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alkoxycarbonyl group containing 2 to 6 carbon atoms, k) a carbamoyl group or carbamoylmethyl group each optionally *N*-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphamoyl or sulphamoylmethyl group each optionally *N*-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, m) an amino group optionally substituted by one or two alkyl groups each containing 1 to 5 carbon atoms, n) 1-pyrrolidinyl or 1-piperidinyl, o) nitro or p) acetamido.

2) Compounds of formula I, as claimed in claim 1, in which both A and B are -O-; g is 1, R₁ is halo or an alkyl group containing 1 to 3 carbon atoms; G₁-G₂-G₃ are -NH-CH=CH-; or -S-C(R'')=C(R''')-; R'' is H and R''' is H or halo; R₂ is H; R₃ and R₄, are both H; U is methylene; Q is a group of formula IIc in which V is methylene, E and E' are both ethylene and R₆ is H; and T is phenyl or 2-, 3- or 4 pyridyl each of which may be optionally substituted by one or more substituents selected from methoxy, nitro, halo or acetamido.

30

3) Compounds of formula I, as claimed in claim 1, selected from:

N-{[1-(9-chloro-2,3-dihydrothieno[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]-methyl}pyridine-2-sulphonamide;

35

N-{[1-(2,3-dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl)piperid-4-yl]methyl}pyridine-2-sulphonamide;

5 4-acetamido-*N*-{[1-(2,3-dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl)piperid-4-yl]-methyl}benzenesulphonamide;

N-{[1-(2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}pyridine-2-sulphonamide

10 *N*-{[1-(2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}pyridine-3-sulphonamide

2,3-dichloro-*N*-{[1-(2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}benzenesulphonamide

15 *N*-{[1-(2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}-2,4-difluorobenzenesulphonamide

20 4-(acetamido)-*N*-{[1-(2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-ylmethyl)piperid-4-yl]methyl}benzenesulphonamide

and pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

25 4) A pharmaceutical composition comprising a compound of formula I, as claimed in claim 1, in conjunction with a pharmaceutically acceptable diluent or carrier.

5) A compound of formula I, as claimed in claim 1, for use as a medicament.

30 6) A compound of formula I, as claimed in claim 1, for use in the treatment of depression, anxiety, psychoses, tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders, anorexia, cardiovascular and
35 cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, and spasticity.

7) Use of a compound of formula I, as claimed in claim 1, in the manufacture of a medicament for treating depression, anxiety, psychoses, tardive dyskinesia, Parkinson's
40 disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-

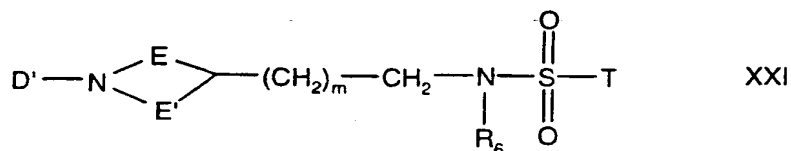
compulsive behaviour, panic attacks, social phobias, eating disorders and anorexia, cardiovascular and cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, or spasticity.

5

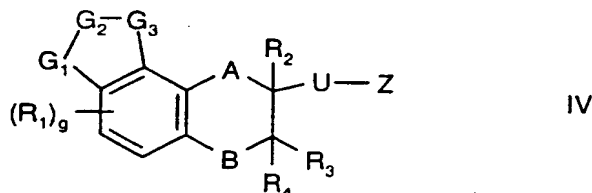
- 8) A method of treating depression, anxiety, psychoses, tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders and anorexia, cardiovascular and cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, or spasticity in human beings, which comprises the administration of a therapeutically effective amount of a compound of formula I, as claimed in claim 1, to a patient in need thereof.

15

- 9) A process for the preparation of compounds of formula I, as claimed in claim 1, in which Q is a group of formula IIc, comprising the reaction of a compound of formula XXI



- 20 in which D' is H and m is 0, 1 or 2, with a compound of formula IV



in which Z is a leaving group, optionally in the presence of a base, and optionally in a solvent

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/07035

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D495/04 A61K31/38 A61K31/44 A61K31/34 C07D491/056
C07D493/04 //(C07D495/04, 333:00, 319:00), (C07D491/056, 319:00,
209:00), (C07D493/04, 319:00, 307:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 07274 A (BOOTS) 16 March 1995 see claims 1,15 ---	1,4
A	EP 0 352 613 A (BAYER) 31 January 1990 see claims 1,13 ---	1,4
P,A	WO 97 23485 A (KNOLL) 3 July 1997 see claims 1,8 -----	1,4

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

13 May 1998

Date of mailing of the international search report

22.05.98

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Authorized officer

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 97/07035

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Please see attached sheet ./.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/EP 97/07035

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